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U.S. Patent Application 09/923,327

Inventors: Patricia Murphy et al.

Filed: August 8, 2001

Title: Determining Common Functional Alleles in a Population and Uses therefor

Group Art Unit: 1634

Examiner: Stephanie Zitomer, Ph.D.

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Copy of pending claims 1-90 attached

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Attorney Docket No. 5371.16.US01

WHAT IS CLAIMED IS:

1. A method of determining a functional allele profile of a gene in a population, comprising:
  - (a) identifying the nucleotide sequence of a gene of interest out of genomic DNA from each of a population of individuals identified as having a family history which indicates inheritance of functional alleles of the gene of interest;
  - (b) identifying the haplotype sequence of at least one individual identified as having a family history which indicates inheritance of only functional alleles of a gene of interest;
  - (c) if any heterozygous sequence is identified in step (a), then subtracting the haplotype sequence identified in (b) from said heterozygous sequence to identify the ~~companion haplotype to the haplotype identified in step (b);~~
  - (d) ~~determining the frequency of occurrence of the haplotypes determined in~~ steps (b) and (c); and
  - (e) rank ordering the frequency of occurrence of each haplotype, whereby the identity of the alleles containing each haplotype and the determination of their relative frequencies constitutes the functional allele profile of the gene of interest in the population.
2. ~~The method of claim 1 wherein a haplotype is identified in step (b) by~~ determining the sequence of a homozygous individual.
3. The method of claim 2 wherein the sequence of the homozygous individual is identified in step (a).
4. ~~The method of claim 2 wherein the sequence of the homozygous individual is~~ obtained from an individual not among the individuals identified in step (a).
5. The method of claim 1 wherein a haplotype is identified in step (b) by sequencing analysis of a cDNA sample.

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6. The method of claim 5 wherein the cDNA sample is obtained from an individual whose sequence is identified in step (a).

7. The method of claim 5 wherein the cDNA sample is obtained from an individual not among the population in step (a).

8. The method of claim 1 wherein at least one family history in step (a) is determined by pedigree analysis.

9. The method of claim 1 wherein at least one family history in step (a) is determined by questionnaire.

10. The method of claim 1 wherein at least one genomic sequence of step (a) contains all exons of the gene.

11. The method of claim 1 wherein at least one genomic sequence of step (a) contains intronic sequences.

12. The method of claim 10 or 11 wherein at least one genomic sequence of individual amplified exons is identified.

13. A method of determining the consensus functional sequence of a gene in a population, comprising:

(a) identifying the sequence of a gene of interest out of genomic DNA from each of a population of individuals identified as having a family history which indicates inheritance of functional alleles of the gene of interest;

(b) identifying the haplotype sequence of at least one individual identified as having a family history which indicates inheritance of only functional alleles of a gene of interest;

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(c) if any heterozygous sequence is identified in step (a), then subtracting the haplotype sequence identified in (b) from said heterozygous sequence to identify the companion haplotype to the haplotype identified in step (b);

(d) determining the frequency of occurrence of the haplotypes determined in steps (b) and (c); and

(e) rank ordering the frequency of occurrence of each haplotype, whereby the most frequently occurring sequence is the consensus functional sequence of the gene in the population.

14. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 13 wherein the population in step (a) contains at least five individuals.

15. A method of determining a functional allele profile comprising, in this order:

(a) determining the nucleotide sequence of at least one allele containing the nucleotide sequence of an isolated coding region of a gene of interest from a single individual identified as having a family history which indicates inheritance of functional alleles of the gene of interest;

(b) ~~determining the genomic sequence of the same gene of interest inclusive of any naturally occurring polymorphisms from a subpopulation of at least five unrelated individuals; other than the individual in step (a), identified as having a family history~~ which indicates inheritance of functional alleles of the gene of interest;

(c) subtracting the sequence in (a) from the sequence identified in (b) for all individuals tested, such that the sequence remaining after subtraction determines the companion allele to the allele in (a);

(d) if the sequence determined in (a) is not present among the sequences determined in (b), ~~determining an alternative allele having a haplotype for comparison and subtraction in the individuals in (b) by identifying at least one individual among the~~ population in (b) homozygous for the allele having said haplotype;

(e) determining the frequency of occurrence of the allele determined in (a); (c) and (d) among the samples in (b); and

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(f) rank ordering the frequency of occurrence of the alleles to obtain a "functional allele profile" for the gene of interest.

16. A method of determining the consensus functional sequence of a gene in a population, comprising in this order:

(a) determining the nucleotide sequence of at least one allele containing the nucleotide sequence of an isolated coding region of a gene of interest from a single individual identified as having a family history which indicates inheritance of functional alleles of the gene of interest;

(b) determining the genomic sequence of the same gene of interest inclusive of any naturally occurring polymorphisms from a subpopulation of at least five unrelated individuals other than the individual in step (a), identified as having a family history which indicates inheritance of functional alleles of the gene of interest;

(c) subtracting the sequence in (a) from the sequence identified in (b) for all individuals tested, such that the sequence remaining after subtraction determines the companion allele to the allele in (a);

(d) if the sequence determined in (a) is not present among the sequences determined in (b), determining an alternative allele having a haplotype for comparison and subtraction in the individuals in (b) by identifying at least one individual among the population in (b) homozygous for the allele having said haplotype;

(e) determining the frequency of occurrence of the allele determined in (a), (c) and (d) among the samples in (b); and

(f) rank ordering the frequency of occurrence of the alleles, whereby the most frequently occurring sequence is the consensus functional sequence of the gene in the population.

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17. The method of claim 1, 13, 15, or 16 wherein the gene of interest has at least 5 naturally occurring polymorphisms of frequencies of at least 10% in the population.

18. A method for determining a new haplotype of a gene of interest where at least one wild-type nucleotide sequence of said gene of interest is known comprising the steps of:

(a) selecting at least one individual having a genetic history which indicates inheritance of functional alleles of the gene of interest.

(b) determining a nucleotide sequence of said gene, or a fragment thereof, in at least one allele of said individual.

(c) comparing each nucleotide sequence from said individual to that of each wild-type nucleotide sequence wherein the presence of at least one nucleotide sequence different from each known wild-type nucleotide sequence indicates the presence of said new haplotype and

if said new haplotype is not determined by step (c), repeating steps (a), (b) and (c) with a different individual until said new haplotype is determined.

19. The method according to claim 18 wherein at least five individuals are selected.

20. The method according to claim 18 wherein said individual is a human.

21. The method according to claim 18 wherein said new haplotype encodes a protein having at least one amino acid difference in its deduced amino acid sequence from a protein encoded by said at least one wild-type nucleotide sequence.

22. An isolated protein encoded by said new haplotype determinable by the method of claim 21.

23. An isolated DNA comprising the nucleotide sequence of said new haplotype of said gene of interest determinable by the method of claim 18.

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24. A DNA comprising the nucleotide sequence of said new haplotype of said gene of interest discovered by the method of claim 18.

25. An isolated DNA comprising a fragment of the nucleotide sequence of said new haplotype of said gene of interest determinable by the method of claim 18, wherein said fragment contains a nucleotide sequence having at least one polymorphic nucleotide.

26. A method for determining a new wild-type amino acid sequence of a protein of interest where at least one wild-type amino acid sequence of said protein of interest is known comprising the steps of:

(a) selecting at least one individual having a genetic history which indicates inheritance of functional alleles of a gene encoding said protein of interest,

(b) determining or deducing at least one amino acid sequence of said protein produced by said individual,

(c) comparing each of said amino acid sequence from said individual to that of each wild-type amino acid sequence, wherein the presence of at least one amino acid difference from each known wild-type amino acid sequence indicates the presence of said new wild-type amino acid sequence and

if said new wild type amino acid sequence is not determined by step (c), repeating steps (a), (b) and (c) with a different individual until said new amino acid sequence for said protein of interest is determined.

27. The method according to claim 26 wherein at least five individuals are selected.

28. The method according to claim 26 wherein said individual is a human.

29. An isolated protein having said new amino acid sequence of said protein of interest determinable by the method of claim 26.

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30. An method for determining a haplotype of a gene of interest for an individual comprising:

- (a) determining a nucleotide sequence of at least a portion of an allele of said gene of interest in regions of said gene containing all polymorphic nucleotides constituting the haplotype in a sample from said individual,
- (b) comparing the nucleotide sequence, or the polymorphic nucleotides, to at least two haplotypes of said gene in the sample, and
- (c) determining the haplotype of said allele of said gene of interest from said sample.

31. The method according to claim 30 wherein said individual is a human.

32. A method for determining a wild-type amino acid sequence for a protein of interest for an individual comprising:

- (a) determining or deducing at least one amino acid sequence of said protein of interest from a sample from said individual, and
- (b) comparing the amino acid sequence obtained to at least two known wild-type amino acid sequences, thereby determining the amino acid sequence present in the individual.

33. The method according to claim 32 wherein said individual is a human.

34. A method for determining a new polymorphism of a gene of interest where at least one wild-type nucleotide sequence of said gene of interest is known comprising the steps of:

- (a) selecting at least one individual having a genetic history which indicates inheritance of functional alleles of the gene of interest,
- (b) determining a nucleotide sequence of said gene, or a fragment thereof, in at least one allele of said individual,
- (c) comparing each nucleotide sequence from said individual to that of each wild-type nucleotide sequence, wherein the presence of at least one nucleotide sequence



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different from each known wild-type nucleotide sequence indicates the presence of said new polymorphism, and

if said new polymorphism is not determined by step (c), repeating steps (a), (b) and (c) with a different individual until said new polymorphism is determined.

35. The method according to claim 34 wherein at least five individuals are selected.

36. The method according to claim 34 wherein said individual is a human.

37. The method according to claim 34 wherein said gene having the new polymorphism encodes a protein having at least one amino acid difference in its deduced amino acid sequence from a protein encoded by said at least one wild-type nucleotide sequence.

38. An isolated protein encoded by said gene having a new polymorphism determinable by the method of claim 37.

39. An isolated DNA comprising the nucleotide sequence of said gene having the new polymorphism determinable by the method of claim 34.

40. A DNA comprising the nucleotide sequence of said gene having the new polymorphism discovered by the method of claim 34.

41. A method for determining a combination of a haplotype for a first gene of interest and at least one polymorphism in a second gene of interest comprising:

(a) determining the haplotype of an allele of said first gene of interest in an individual,

(b) determining the nucleotide sequence of each polymorphism of an allele of the second gene of interest in the same individual, and

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(c) identifying a combination of the haplotype of said first gene and the polymorphism of the second gene for the same individual.

42. The method according to claim 41 wherein said at least one polymorphism determines a haplotype for said second gene of interest.

43. The method according to claim 41 wherein said combination indicates a condition or a susceptibility to a condition.

44. An antibody capable of either binding to either said isolated protein having said new amino acid sequence according to claim 29 or a protein having a known wild-type amino acid sequence, but not both under the same binding conditions.

45. An antibody according to claim 44 bound to a label.

46. An immunoassay capable of distinguishing between a protein having one wild-type amino acid sequence and a protein having a variant wild-type amino acid sequence comprising:

(a) contacting the antibody according to claim 44 with a sample containing at least one of said proteins, and

(b) detecting the presence or absence of binding between said antibody and said protein.

47. A method for determining whether to administer a composition to an individual for a particular use comprising:

(a) determining the nucleotide sequence of at least one polymorphism of a gene of interest, and

(b) reporting a result indicating the appropriateness of administering the composition to the individual for the particular use,

wherein the presence of at least one polymorphic form of the gene of interest determines the need for or provides a different response to the composition for a particular use from at least one other polymorphic form of the gene of interest.

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48. The method according to claim 47 wherein said at least one polymorphism defines a haplotype.

49. The method according to claim 47 wherein said composition is a pharmaceutical.

50. A method for determining a trait, condition or susceptibility to a condition associated with a gene of interest comprising:

(a) determining the nucleotide sequence of at least one polymorphism of the gene of interest, and

(b) reporting a result indicating the presence of said trait, condition or susceptibility to the condition,

wherein the presence of at least one polymorphic form of the gene of interest determines the trait, condition or susceptibility for the condition from at least one other polymorphic form of the gene of interest.

51. The method according to claim 47 wherein said at least one polymorphism defines a haplotype.

52. An oligonucleotide, or its complement, capable of recognizing a polymorphism in a gene of interest by hybridizing to one polymorphic form of said gene but not another polymorphic form under the same hybridizing conditions.

53. A panel of oligonucleotides according to claim 52 wherein the panel comprises at least one oligonucleotide for each polymorphism constituting a haplotype for said gene of interest.

54. A probe chip for determining the presence or absence of a particular nucleotide at a particular polymorphism determined by the method of claim 34 in a desired gene or fragment thereof, comprising:

(a) a solid phase and

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(b) a plurality of oligonucleotide probes,  
wherein the probes are immobilized on the solid phase,  
wherein the probes comprise at least "n" groups of oligonucleotide probes,  
wherein each unique probe within the group of oligonucleotide probes is  
complementary to said desired gene or fragment thereof, and contains a nucleotide  
complementary to said particular polymorphism in said desired polynucleotide at a  
different position within said unique probe, and  
wherein "n" is an integer greater than 0

55. The probe chip according to claim 54, further comprising an additional group  
of complementary probes which are complementary to said group of probes and capable  
of hybridizing to a complementary strand of said desired gene or fragment thereof.

56. A method for determining a new polymorphism in a gene comprising the  
steps of:

- (a) selecting at least one individual having a genetic history which indicates  
inheritance of functional alleles of the gene,
- (b) obtaining a sample of genomic DNA from said at least one individual,
- (c) determining a nucleotide sequence of at least a fragment of at least one allele  
of said gene in said individual,
- (d) comparing each nucleotide sequence from said at least a fragment said allele to  
that of at least one wild-type nucleotide sequence of said gene or fragment, wherein the  
presence of at least one nucleotide difference from each known wild-type nucleotide  
sequence indicates the presence of said new polymorphism, and  
if said new polymorphism is not determined by step (c), repeating steps (a), (b)  
and (c) with a different individual until said new polymorphism is determined.

57. The method according to claim 56 wherein at least five individuals are  
selected.

58. The method according to claim 56 wherein said individual is a human.

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59. The method according to claim 56 wherein said gene having the new polymorphism encodes a protein having at least one amino acid difference in its deduced amino acid sequence from a protein encoded by said at least one wild-type nucleotide sequence.

60. An isolated protein encoded by said gene having a new polymorphism determinable by the method of claim 59.

61. An isolated DNA comprising the nucleotide sequence of said gene having the new polymorphism determinable by the method of claim 56.

62. A DNA comprising the nucleotide sequence of said gene having the new polymorphism discovered by the method of claim 56.

63. A method for determining a new haplotype of a gene of interest wherein said haplotype comprises at least two single nucleotide polymorphisms which identify an allele that occurs in the total normal population, comprising the steps of:

- (a) selecting at least one individual having a genetic history which indicates inheritance of functional alleles of the gene,
  - (b) obtaining a sample of genomic DNA from at least one said individual,
  - (c) determining a nucleotide sequence of at least a fragment of at least one allele of said gene in said individual,
  - (d) comparing each nucleotide sequence from at least a fragment of said allele to that of at least one wild-type nucleotide sequence of said gene or fragment, wherein the presence of at least two nucleotide differences from each known wild-type nucleotide sequence indicates the presence of said new haplotype, and
- if said new haplotype is not determined by step (c), repeating steps (a), (b) and (c) with a different individual until said new haplotype is determined.

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64. A method according to claim 63 wherein the allele occurs in at least 10% of the total normal population.

65. A method according to claim 63 wherein the allele occurs in at least 10% of the normal Caucasian population.

66. A method according to claim 63 wherein the allele occurs in at least 10% of the normal Black/African American population.

67. A method according to claim 63 wherein the allele occurs in at least 10% of the normal Asian population.

68. A method according to claim 63, 64, 65, 66 or 67 wherein said new haplotype encodes a protein having at least one amino acid difference in its deduced amino acid sequence from a protein encoded by at least one wild-type nucleotide sequence.

69. An isolated protein encoded by said new haplotype determinable by the method of claim 63, 64, 65, 66 or 67.

70. An isolated DNA comprising the nucleotide sequence of said new haplotype of said gene of interest determinable by the method of claim 63, 64, 65, 66 or 67.

71. An isolated DNA comprising a fragment of the nucleotide sequence of said new haplotype of said gene of interest determinable the method of claim 63, 64, 65, 66 or 67, wherein said fragment contains a nucleotide sequence having at least two polymorphic nucleotides.

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72. A method for determining a new haplotype of a gene of interest wherein said haplotype comprises at least two single nucleotide polymorphisms which identify an allele which is associated with an increased risk of identified disease in the total normal population, comprising the steps of:

- (a) selecting at least one individual having a genetic history which indicates inheritance of functional alleles of the gene,
  - (b) obtaining a sample of genomic DNA from at least one said individual,
  - (c) determining a nucleotide sequence of at least a fragment of at least one allele of said gene in said individual,
  - (d) comparing each nucleotide sequence from at least a fragment of said allele to that of at least one wild-type nucleotide sequence of said gene or fragment, wherein the presence of at least two nucleotide differences from each known wild-type nucleotide sequence indicates the presence of said new haplotype, and
- if said new haplotype is not determined by step (c), repeating steps (a), (b) and (c) with a different individual until said new haplotype is determined.

73. A method according to claim 72 wherein the allele occurs in at least 10% of the total normal population.

74. A method according to claim 72 wherein the allele occurs in at least 10% of the normal Caucasian population.

75. A method according to claim 72 wherein the allele occurs in at least 10% of the normal Black/African American population.

76. A method according to claim 72 wherein the allele occurs in at least 10% of

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the normal Asian population.

77. A method according to claim 72, 73, 74, 75 or 76 wherein said new haplotype encodes a protein having at least one amino acid difference in its deduced amino acid sequence from a protein encoded by at least one wild-type nucleotide sequence.

78. An isolated protein encoded by said new haplotype determinable by the method of claim 72, 73, 74, 75 or 76.

79. An isolated DNA comprising the nucleotide sequence of said new haplotype of said gene of interest determinable by the method of claim 72, 73, 74, 75 or 76.

80. An isolated DNA comprising a fragment of the nucleotide sequence of said new haplotype of said gene of interest determinable the method of claim 72, 73, 74, 75 or 76, wherein said fragment contains a nucleotide sequence having at least two polymorphic nucleotides.

81. A method for determining a plurality of haplotypes of a gene of interest wherein said haplotypes collectively define the alleles of said gene in a normal population, and wherein each said allele comprises at least two single nucleotide polymorphisms, comprising the steps of:

(a) selecting at least one individual having a genetic history which indicates inheritance of functional alleles of the gene;

(b) obtaining a sample of genomic DNA from at least one said individual,

(c) determining a nucleotide sequence of at least a fragment of at least one allele of said gene in said individual,

(d) comparing each nucleotide sequence from at least a fragment of said allele to



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that of at least one wild-type nucleotide sequence of said gene or fragment, wherein the presence of at least two nucleotide differences from each known wild-type nucleotide sequence indicates the presence of said new haplotype, and

if said new haplotype is not determined by step (c), repeating steps (a), (b) and (c) with a different individual until said new haplotype is determined.

82. A method according to claim 81 wherein the population is the normal Caucasian population.

83. A method according to claim 81 wherein the population is the normal Black/African American population.

84. A method according to claim 81 wherein the population is the normal Asian population.

85. A method for determining a set of haplotypes of defined alleles from contiguous genes within the same region of a chromosome in the total population:

(a) selecting at least one individual having a genetic history which indicates inheritance of functional alleles of the gene,

(b) obtaining a sample of genomic DNA from at least one said individual,

(c) determining a nucleotide sequence of at least a fragment of at least one allele of said gene in said individual,

(d) comparing each nucleotide sequence from at least a fragment of said allele to that of at least one wild-type nucleotide sequence of said gene or fragment, wherein the presence of at least two nucleotide differences from each known wild-type nucleotide sequence indicates the presence of said new haplotype, and

if said new haplotype is not determined by step (c), repeating steps (a), (b) and (c)

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with a different individual until said new haplotype is determined.

86. A method according to claim 85 wherein the population is the normal Caucasian population.

87. A method according to claim 85 wherein the population is the normal Black/African American population.

88. A method according to claim 85 wherein the population is the normal Asian population.

89. A method for determining a set of haplotypes of defined alleles from non-contiguous genes from different regions of a chromosome in the total population, comprising the steps of:

(a) selecting at least one individual having a genetic history which indicates inheritance of functional alleles of the gene;

(b) obtaining a sample of genomic DNA from at least one said individual;

(c) determining a nucleotide sequence of at least a fragment of at least one allele of said gene in said individual,

(d) comparing each nucleotide sequence from at least a fragment of said allele to that of at least one wild-type nucleotide sequence of said gene or fragment, wherein the presence of at least two nucleotide differences from each known wild-type nucleotide sequence indicates the presence of said new haplotype, and

if said new haplotype is not determined by step (c), repeating steps (a), (b) and (c) with a different individual until said new haplotype is determined.

90. A method according to claim 89 wherein the population is the normal

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Caucasian population.

91. A method according to claim 89 wherein the population is the normal Black/African American population.

92. A method according to claim 89 wherein the population is the normal Asian population.

93. A method for determining a set of haplotypes of defined alleles from non-contiguous genes from different chromosomes in the total population, said method comprising the steps of:

(a) selecting at least one individual having a genetic history which indicates inheritance of functional alleles of the gene,

(b) obtaining a sample of genomic DNA from at least one said individual,

(c) determining a nucleotide sequence of at least a fragment of at least one allele of said gene in said individual,

(d) comparing each nucleotide sequence from at least a fragment of said allele to that of at least one wild-type nucleotide sequence of said gene or fragment, wherein the presence of at least two nucleotide differences from each known wild-type nucleotide sequence indicates the presence of said new haplotype, and

if said new haplotype is not determined by step (c), repeating steps (a), (b) and (c) with a different individual until said new haplotype is determined.

94. A method according to claim 89 wherein the population is the normal Caucasian population.

95. A method according to claim 89 wherein the population is the normal

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Black/African American population.

96. A method according to claim 89 wherein the population is the normal Asian population.